REMARKS

Applicants address the examiner's remarks in the order presented in the Office Action (dated April 27, 2006). All claim amendments are made without prejudice and do not represent acquiescence in any ground of rejection.

Applicants acknowledge with appreciation the time and courtesies extended by the examiner toward applicants' representative during the October 18, 2006 telephone interview conducted with inventor B. Brett Finlay and applicants' representative. The examiner's insights and comments have advanced the prosecution of the case. In particular, the outstanding rejections were discussed. The Kobayashi reference was discussed in detail. Further discussion involved potential claim amendments in view of same and ways this matter can move forward.

STATUS OF THE CLAIMS

Claims 33-90 are pending. Claims 79-82 were canceled. Claims 33, 34, 46, 48, 60, 62, 63, 69, 77, 83-85, 87, 89, and 90 were amended. Claims 91-116 are new. Therefore, claims 33-78 and 83-116 will be pending after entry of this amendment.

Support for the claim amendments can be found in the claims as originally filed and throughout the specification. Multiple dependent claims were amended to proper form. For example, support for the amendments to claims 33 and 34 can be found at page 24, in Example 1, lines 23-25. Support for the "concentrated" language in claims 105, 106, 108, and 112, can be found, for example, at page 16, line 7. For example, support for EHEC serotype language in claims 109 and 113 can be found, for example, at page 15, lines 11-15. Support for the routes of administration language in claims 110, 114, 115, and 116 can be found, for example, at page 23, lines 21-22. No new matter will be added by entry of this amendment.

The specification was objected to because of the following informalities: trademarks Emulsigen Plus, VSA3 and Amphigen should be capitalized wherever it appears in the specification and be accompanied by the generic terminology.

The use of the trademarks Emulsigen Plus, VSA3 and Amphigen have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology

Claims 46, 48, 60, 62, 69, 79, 80, 81 and 82 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claims 33, 34, 37, 42, 51, 56, 63, and 73 stand rejected under 35 U.S.C. § 102(b) as anticipated by Kobayashi (JP 59020226, published February 1, 1984; translation provided by the examiner).

Claims 33, 34, 37, 38, 42, 51, 52, 56, 63, and 73 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Wilson et al. (Journal of Food Protection, 60(11):1451-1453, 1997).

Claims 33, 34, 37, 38, 42, 51, 52, 56, 63, and 73 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Bochner (U.S. Patent 6,136,554, issued October 24, 2000 and filed March 17, 1997).

Claims 33, 34, 37, 40, 51, 54, 63, 64, 74, 77, 78 and 83-85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Harlos et al. (Antibodies: A Laboratory Manual, Cold Spring Harbor Pres, 1988, pages 96-99).

Claims 33, 34, 37, 42, 51, 56, 63, 64 and 65 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of in view of Morein et al (Methods: A Companion to Methods in Enzymology, 19(10:94-102, 1999).

Claims 33, 34, 37, 40, 51, 54, 56, 63, 64, 65, 69, 71, 74, 76, 77, 78, and 79 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Allison (Methods: A companion to Methods of Enzymology, 19:87-93, 1999).

Claims 33, 34, 37, 40, 42, 43, 44, 51, 54, 56, 57, 58, 63, 64, 65, 69, 71, 72, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 and 85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Pokric, Periodicum Biologorium 101(4):823-3-2, 1999).

Claims 33, 34, 37, 40, 41, 42, 43, 44, 51, 54, 55, 56, 57, 58, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 79, 80, 81, 82, 86, 87, 88 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Little-van den Hurk et al (U.S. Patent 5,951, 988 issued September 14, 1999, filed June 5, 1995).

Claims 47, 48, 61, 62 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of Pokric as applied to claims 33, 34, 37, 40, 42, 43, 44, 51, 56, 57, 58, 63, 64, 65, 69, 71, 72, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, and 85 above, and further in view of Finlay (WO 99/24576 published May 20, 1999).

Claims 33, 34, 45, 36, 37, 40, 45, 46, 49, 50, 51, 54, 56, 59, 60, 63, 64, 65, 69, 71, 74, 76, 77, 78, 79, and 89 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi in view of in view of Finlay (WO 99/24576 published May 20, 1999).

Claim 90 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kokayashi and of Finlay (WO 99/24576 published May 20, 1999) as applied to claims 33, 34, 35, 36, 37, 40, 45, 46, 49, 50, 51, 54, 56, 59, 60, 63, 64, 65, 69, 71, 74, 76, 77, 78, 79, and 89 above, and further in view of Kudva (Diss Abstr. Int., B 1998, 58(10):5252).

SPECIFICATION

The disclosure was objected to because the use of the trademarks EMULSIGEN PLUS™, VSA3 and AMPHIGEN™ were been noted as being listed incorrectly in the specification. The examiner requested that these terms should be capitalized wherever they appear and be accompanied by the generic terminology.

Applicants' representative has amended the specification. More specifically, applicants' representative capitalized AMPHIGEN™ and added the generic terminology after the first occurrence of AMPHIGEN™.

Applicants' representative believes the occurrence of EMULSIGEN PLUS™ and VSA3 is correct in the specification as filed. Applicants' representative welcomes additional clarification from the examiner if this understanding is in error.

At least for these reasons and in view of the amendments to the specification, Applicants request that the objection to the specification be removed.

35 U.S.C. § 112, SECOND PARAGRAPH (INDEFINITENESS)

Claims 46, 48, 60, 62, 69, 79, 80, 81 and 82 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

The examiner stated that the term "the cell protein" in claims 46, 48, 60 and 62 lacks antecedent basis in the claims. In addition, the examiner stated that the recitation renders the metes and bounds of the claim uninterpretable, because the composition comprises the cell supernatant and not the E. coli cell *per se*.

Without acceding to the propriety of the rejection of pending claims 46, 48, 60, 62, 69, 79, 80, 81 and 82, applicants cancelled claims 79-82 and amended claims 46, 48, 60 and 62. Applicants therefore respectfully request reconsideration of the claims as amended. For

these reasons, applicants request the examiner withdraw the rejection of pending claims claims 46, 48, 60, 62, 69, 79, 80, 81 and 82 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

35 U.S.C. § 102(B)

Claims 33, 34, 37, 42, 51, 56, 63, and 73 stand rejected under 35 U.S.C. § 102(b) as anticipated by Kobayashi (JP 59020226, published February 1, 1984; translation provided). The examiner has yet to show that the Kobayashi referenced anticipates the claimed invention.

For a rejection under § 102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

According to the examiner, Kobayashi teaches a vaccine comprising supernatant from a vero cyst toxic strain of E. coli wherein the strain is culture by percolation and the upper supernatant liquid is centrifugally separated, percolated through a 0.45 μm filter, formalin is added to obtain an supernatant immunogen. The vero cyst toxic immunogen is admixed with

that obtained from cilia and the adjuvant aluminum gel is added preparing an inactivated vaccine. The vaccine is vaccinated subcutaneously or inside the muscle 2-3 times every other week (see pages 12-14 of the translation) to pregnant pigs. According to the examiner, applicants' specification acknowledges at page 1, lines 17-20, that enterohaemmorragic E. *coli* (EHEC) are also called Shiga toxin E. coli (STEC) and verotoxigenic E. coli (VTEC). The examiner concluded that the vero cyst toxic strain of Kobayashi is therefore necessarily enterohemorrhagic. In addition, the examiner stated that Kobayashi teaches that a vaccine that is effective for all of the colon bacillus diarrhea would have to have enterotoxins (LT or ST), cilia and vero cyst toxicity (citing Kobayashi, page 9). Applicants traverse for the following reasons.

Kobayashi is focused on a completely different E. coli that causes a very different disease in pigs. Kobayashi uses (very old) technology to grow up E. coli in standard bacteria media, then harvests the supernatants, which contains toxins (LT, and ST) and pili (K88, K99). Kobayashi then formalin fix the supernatant and use that (this is probably the oldest bacterial vaccine technology other than growing up whole cells and fixing them- for example, this is the original way diphtheria vaccine is made, back in the late 1800's.)

Kobayashi differs from the instant application in the following ways: a) they are immunizing directly to block a pig disease with parts of a pig pathogen (applicants are not trying to block cow disease with a cow pathogen (O157 does not affect cows), but block human disease by immunizing cows). Secondly, it is well known that the pig pathogens disclosed in Kobayashi secrete these toxins, and there is really no special knowledge in growing them up and harvesting supernatant (this has been done for years). Applicants' instant invention is quite different because applicants have to grow the pathogens under

special conditions to induce the type III secreted proteins (usually minimal media), rather than standard media as disclosed by Kobayashi. Applicants discovered that EHEC secretes type III proteins, and there is no report of a vaccine that uses type III secreted proteins, so not obvious thing to do).

A major difference between the Kobayashi disclosure and the instant application is that the instant invention teaches making type III secreted effector proteins, none of which are toxins or pili (Kobayashi refers to pili as cilia). Thus applicants are inducing special (non-toxin) proteins, rather than the well known toxins.

Finally, Kobayashi discloses a very different pathogen (called "entertoxigenic E. coli, or ETEC), and has a completely different set of virulence factors than EHEC. It does not have a type III secretion system nor secrete type III proteins, which EHEC does. In addition, a "verotoxin" as disclosed in Kobayashi and Shiga toxin/verotoxin in EHEC are not the same toxins. As disclosed in the instant application, applicants' vaccine is not about toxins, but the type III secreted proteins, and the Shiga toxin is not secreted by the type III system. Vero cells are particularly sensitive to many different toxins, and have been used for years to assay for toxin activity. Thus "verotoxigenc" is a term applied to several toxins over the years. EHEC Vero toxin is now being called Shiga toxin (ironically also abbreviated as ST), not to be confused with heat Stable Toxin discussed above for ETEC. Applicants' instant invention a) discloses a completely different type of E. coli, b) must grow under special conditions to get the type III secreted proteins produced, c) toxins and pili are not the focus of applicants' vaccine, rather the focus is on type III secreted proteins, and d) applicants are not vaccinating to protect the host animal (cows/pigs), but instead vaccinating carrier animals to prevent human disease.

Accordingly, as the examiner fails to identify anything in Kobayashi that teaches each and every element of the present invention, applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn..

35 U.S.C. § 103(A)

Various groups of claims were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kobayashi together with any combination of the following references: Wilson et al., Bocher (U.S. Patent 6,136,554), Harlow et al., Morein et al, Allison et al., Pokric, Little-van den Hurk, and Findlay (WO 99/24576).

Applicants respectfully request reconsideration and withdrawal of the rejection because the Office has failed to establish *prima facie* obviousness. Applicant's statements above under the anticipation rejection are applicable here. If a single reference is used

To establish *prima facie* obviousness, the examiner must provide ***objective evidence*** that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. "The mere fact that references ***can*** be combined or modified does not render the resultant combination obvious ***unless the prior art also suggests the desirability of the combination***." M.P.E.P. § 2141.03 (citing *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990), emphasis added).

Prior art references that serve as the basis of an obviousness rejection must be considered by the examiner in their entirety, *i.e.*, ***the references must be considered as a whole***, including portions that would lead away from the claimed invention. M.P.E.P. 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

Applicants respectfully submit that the examiner has failed to demonstrate that those of ordinary skill in the art would have been motivated to combine the teachings Kobayashi with the teachings of the other combination of cited references especially in view of applicants' comments above regarding Kobayashi. In fact, based on applicants' statements regarding Kobayashi, Kobayashi is unsuitable for its intended purpose under both §102 and §103. Therefore when one reference falls when used in combination with another reference or combination of references in a 35 U.S.C. §103(a) rejection, the combination is also unsuitable for its intended purpose (when one reference "falls" in the combination of references, all references "fall" in the combination of references).

In other words, since Kobayashi is used in combination with any of the following references, Wilson et al., Bocher (U.S. Patent 6,136,554), Harlow et al., Morein et al., Allison et al., Pokric, Little-van den Hurk, and Findlay (WO 99/24576), each combination is unsatisfactory for its intended purpose in view of the deficiency of Kobayashi for each combination.

Accordingly, applicants submit that a *prima facie* case of obviousness has not been established by the combination of Kobayashi together with any combination of the other references cited by the examiner. Therefore, one skilled in the art would not have been motivated to combine the cited references to arrive at the present invention. For these reasons, applicants request that the examiner withdraw the rejection of pending claims under 35 U.S.C. §103(a).

CONCLUSION

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance.

Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

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